UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/870,762	06/06/97	DUFT	B 226/104

HM32/0916

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EXAMINER	
DEVI,S	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/16/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary

Application No.	Applicant(s)
08/870,762	BJ Duft et al.
Examiner	**Group Art Unit**
S. Devi	1641

☒ Responsive to communication(s) filed on *Apr 17, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6* ~~is~~/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6* ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Effective 7 February 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

2. Acknowledgment is made of Applicants' submission of CRF filed 20 August 1998 (paper no. 6).

3. Acknowledgment is made of Applicants' preliminary amendments to the specification filed 20 August 1998 (paper no. 7).

Specification/Informalities

4. The specification of the instant application is objected to because it contains grammatical/spelling/typographical errors. For example, see page 30, line 12, "weight reduction weight" and page 33, line 17 "rats (200-250) grams".

Claims Rejections - 35 USC §112, first paragraph

5. Claims 1-6 are rejected under 35 USC §112, first paragraph, because the specification while being enabling for a method of treating obesity in a human subject comprising administering an effective amount of an amylin or an amylin agonist, does not reasonably provide enablement for a method of "preventing" obesity in a human subject. Applicants have provided support in the instant specification and examples for a method of "treating" obesity in a human subject comprising administering an effective amount of an amylin or an amylin agonist. However, the disclosure is not supportive of a method of "preventing" obesity in a human subject by administering an effective amount of an amylin or an amylin agonist. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim.

To be commensurate with the scope of the enabling disclosure, it is suggested that Applicants limit the scope of claims 1-6 to a method of treating obesity in a human subject comprising administering an effective amount of an amylin or an amylin agonist.

Claims Rejections - 35 USC §102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1-3 are rejected under 35 U.S.C § 102 (e) as being anticipated by Rink *et al.* (US 5,739,106).

Rink *et al.* teach methods for controlling body weight, reducing food intake and suppressing appetite in mammals including humans using an amylin agonist (abstract and column 11, lines 25 and 26). Rink's claim 85 is drawn to a method for control of body weight in a mammal (inclusive of humans) comprising administering a therapeutically effective amount of an amylin agonist such as ^{25,28,29}pro-h-amylin (column 12, lines 36-39). Rink's claims 83 and 84 are drawn to methods for suppressing food intake and for control of appetite in a mammal (inclusive of humans) comprising administering a therapeutically effective amount of an amylin agonist such as ^{25,28,29}pro-h-amylin (column 12, lines 27-34). Amylin agonist is administered in an amount of about 0.1 μg/kg/day (column 95, lines 1-8). It is also taught that, in both clinical and epidemiological studies, obesity and type 2 diabetes mellitus are associated, and both may have common pathogenetic mechanisms. It is disclosed that weight reduction is often recommended as the first course of action for patients suffering from type II diabetes mellitus (column 1, second paragraph).

Claims 1-3 are anticipated over Rink *et al.*

Claims Rejections - 35 USC §103

8. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person.

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

9. Claims 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rink *et al.* (US 5,739,106) as applied to claim 1 above, and further in view of Gaeta *et al.* (US 5,686,411).

The references of Rink *et al.* and Gaeta *et al.* have been applied in this rejection because they qualify as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly are not disqualified under U.S.C. 103(a).

The teachings of Rink *et al.* have been explained above. Rink *et al.* do not teach the specific doses, times and route of administration recited in claims 4-6.

Gaeta *et al.* teach that "[a]s will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition ..... and other factors". Typical doses contain 0.1 to 1.0 mg of an amylin agonist compound and this range covers the one recited in claim 6. The composition may conveniently be provided in the form suitable for subcutaneous administration (column 7, lines 37-40). It is further taught that a "suitable administration format may best be determined by a medical practitioner for each patient individually" (column 7, lines 45-47), and that suitable "doses are readily determined by those in the art" (column 8, lines 62 and 63).

Further, the specific time period of administration is generally dose dependent and the time is determined based on standard treatment regimens. Generally, the dosage and periods of administration would vary with the age, sex, clinical condition, extent of the disease in the patient and can be further determined by one skilled in the art. The dosage and time period can also be

determined or adjusted by a physician on an individual basis. The different times and route of administration can be determined by routine experimentation and thus would have been obvious to one skilled in the art.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Rink's method of controlling body weight, reducing food intake and suppressing appetite in mammals including humans by administering an amylin agonist at doses, time periods and the route recited in the instant claims since these can be readily determined based on the weight, age and physical condition of the patient as taught by Gaeta *et al.* or by routine experimentation.

Claims 4-6 are obvious over the prior art of record.

10. Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996) (I) or Kolterman *et al.* (WO 96/40220) (II) or Moyses *et al.* (*Diabetic Med.* 13 (suppl. 1): 34-38, September, 1996) or Thompson *et al.* (*Diabetes* 46: 632-636, April 1997) in view of Cooper *et al.* (*Biochim. Biophys. Acta* 1014(3): 247-258, 1989, abstract) and Rink *et al.* (US 5,739,106).

Kolterman *et al.* (I) teach a method of treatment of patients with diabetes mellitus by subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e. ^{25,28,29}pro-h-amylin) three times a day (abstract and page 493).

Kolterman *et al.* (II) teach methods of treating type II diabetes mellitus comprising administering a therapeutically effective amount of an amylin agonist such as ^{25,28,29}pro-h-amylin, s-calcitonin and h-amylin (abstract and claims). ^{25,28,29}pro-h-amylin has been found to possess more desirable solubility and stability characteristics compared to human amylin (page 13). It is taught that a suitable administration format may best be determined by a medical practitioner for each patient individually (page 19). "The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range as well as upon the age, weight and condition of the individual". Administration may be preferably by subcutaneous injection. Amylin agonists such as ^{25,28,29}pro-h-amylin may be administered in single or multiple doses, for example, two (BID), three (TID), and/or four

(QID) times per day. BID doses range from about 30 μg to 150 μg BID, more preferably from about 50 μg to 60 μg BID. TID doses range from about 30 μg to 150 μg, more preferably about 60 μg TID. QID doses range from about 30 μg to 60 μg QID, more preferably about 30 μg QID. These doses have been demonstrated to be effective in various human clinical trials and are administered subcutaneously (page 21).

Moyses *et al.* teach a method of treatment of human diabetic patients comprising administering pramlintide ($^{25, 28, 29}$pro-h-amylin) by subcutaneous injections in doses of 30 μg, 100 μg or 300 μg t.i.d. (pages 36 and 38).

Thompson *et al.* teach a method of treating human subjects with diabetes, a clinical condition often associated with obesity, by administering subcutaneously 10, 30 or 100 micrograms (which falls in the dose range recited in claim 6) q.i.d. of Pramlintide, an amylin agonist analogue which "incorporates proline substitutions at positions 25, 28 and 29 of the amylin molecule" (see page 632).

Kolterman *et al.* or Kolterman *et al.* or Moyses *et al.* do not teach a method of treating or preventing obesity by administering pramlintide to a human subject.

Rink *et al.* teach the therapeutic effectiveness of $^{25, 28, 29}$pro-h-amylin, an amylin agonist, in controlling body weight, reducing food intake and suppressing appetite in mammals including humans (abstract and column 11, lines 25 and 26).

Cooper *et al.* teach that "obesity which frequently accompanies" type 2 or non-insulin dependent diabetes mellitus (NIDDM) is a result of, rather than a risk factor for, NIDDM (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's method (I and II) or Moyses' or Thompson's method of treating type 2 diabetes, which is frequently associated with overweight, with $^{25, 28, 29}$pro-h-amylin to treat obesity because, Rink *et al.* teach that $^{25, 28, 29}$pro-h-amylin is also effective in controlling body weight, reducing food intake and suppressing appetite in humans, and that there is an art-recognized clinical need for weight reduction in patients suffering from type II diabetes mellitus. Since Cooper *et al.* teach that obesity is a result of NIDDM or type II diabetes, one of ordinary skill in

the art would be motivated to produce the instant invention for the expected benefit of preventing NIDDM from advancing to or resulting in obesity. One of ordinary skill in the art would have had a reasonable expectation of success in using Kolterman's (I and II) or Moyses' or Thompson's method of treating type II diabetes also for treatment of obesity because these two associated clinical conditions share the common pathogenetic mechanisms as taught by Rink *et al.*

Claims 1-6 as a whole are obvious over the prior art of record.

Conclusion

11. No claims are allowed.

12. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure:

- Weisser *et al.* (*J. Clin. Pharmacol.* 37(6): 453-473, 19 June 1997) teach the association between amylin and obesity and the possible role of amylin in weight reduction (page 467).
- Morley *et al.* (*Am. J. Physiol.* 267: R178-R184, 1994) teach the role of amylin as a peripherally acting satiety agent (abstract).
- Morley *et al.* (*Can. J. Physiol. Pharmacol.* 73: 1042-1046, 1995) teach that amylin decreases food intake in mice and rats when delivered both peripherally and directly into the CNS (abstract).
- Lutz *et al.* (*Physiol. & Behavior* 55(5): 891-895, 1994) teach that low doses of amylin reduces food intake in rats by i.p. injection (abstract).
- Kolterman (*Diabetic Med.* 14(suppl. 1): s35-s38, 13 June 1997) teaches a method of treatment of diabetes mellitus comprising subcutaneous injections of 10, 30 and 100 μg of pramlintide (page s36).
- An article published in *Exp. Opin. Ther. Patents* 4(11): 1383-1384, 1994 discloses amylin and related peptide analogues for a "myriad of therapeutic applications" including treatment of obesity (pages 1383 and 1384).
- Koopman *et al.* (*Neth. J. Med.* 41(1-2): 82-90, 1992) suggest the involvement of amylin in the pathophysiology of obesity, type II diabetes and insulin resistance (abstract).

- Ludwik (*Wien Klin. Wochenster* 109(11): 379-383, June 6, 1997, abstract) teaches the subcutaneous administration of the amylin agonist, pramlintide, in diabetics and the association between obesity and circulating amylin (abstract).

- Rowland *et al.* (*CNS Drugs* June 7 (6): 419-426, 1997) teach the role of amylin in the treatment of overeating and obesity (abstract and page 422).

- Porte (*Diabetes* 40(2): 166-180, 1991) teaches obesity, its associated insulin resistance and the role of amylin (abstract).

- Young *et al.* (*Drug Dev. Res.* 37: 231-248, 1996) teach that the "search for a pharmaceutically superior compound with the biological actions of human amylin resulted in the identification of [Pro ^{25,28,29}] human amylin, assigned the U.S.-adopted name (USAN), pramlintide" (page 231). Actions occurring with varying doses of amylin include reduction of appetite (page 232).

- Cooper (US 5,124,314) teaches a human amylin composition for treatment of diabetes mellitus (claim 9 and abstract) including type 2 diabetes (column 3, lines 63-66). Amylin is given by parenteral subcutaneous administration (last sentence bridging columns 5 and 6).

- Cooper *et al.* (US 5,80,014) teach a method of treatment of obesity on a subject comprising administering to a mammal an effective amount of an amylin antagonist (claims). One such compound, CGRP8-37, which acts as a partial antagonist is also an amylin agonist (column 11, lines 3-6).

- Janes *et al.* (*Diabetes* 45 (suppl. 2): A865, 1996, p. 235A) teach that amylin is deficient in type I diabetes and some cases of type II diabetes, and that human amylin has a propensity to aggregate and has poor solubility. It is further taught that "different combinations of substitution within the human amylin sequence at positions 25, 28 and 29 with proline residues and at position 18 with an arginine residue were identified which greatly reduced the aggregation and precipitation of human amylin". Pramlintide, also designated [Pro ^{25,28,29}] human amylin or AC137 exhibits the best overall properties. "By substituting three residues of the human amylin sequence with proline, a novel compound was discovered that retains the desired biological activity of human amylin whilst possessing superior physicochemical and other characteristics"

(abstract).

- Gaeta *et al.* (US 5,686,411) teach a method of treatment of diabetes mellitus in a mammal (inclusive of humans) comprising administering a therapeutically effective amount of an agonist analogue of amylin (claim 34) such as ^{25,28,29}pro-h-amylin (claim 35).

- Colburn *et al.* (*J. Clin. Pharmacol.* 36: 13-24, 1996) teach the administration of 30-300 μg of AC137 or ^{25,28,29}pro-h-amylin tripro-human amylin to human subjects with insulin-dependent diabetes mellitus (abstract and page 14).

- Thompson *et al.* (*Abstract Book*, 55th *Annual Meeting and Scientific Sessions*, June 10-13, 1995, Georgia World Congress Center, Atlanta, Georgia. *Diabetes* 44: suppl. 1, May 1995, Ab. 469, p. 127A) teach a method of treating type II diabetic patients comprising subcutaneous injections of AC137 (abstract).

- Morley *et al.* (*Peptides* 12: 865-869, 1991) teach that amylin decreases food intake in both diabetic and non-diabetic mice following intracerebroventricular administration (abstract). Amylin may have both central and peripheral sites of action. Unlike amylin, CGRP, an amylin agonist, only inhibited feeding after central and not after peripheral administration. Amylin is considerably more potent than CGRP at suppressing food intake. Morley *et al.* suggest the possible role of amylin in the pathophysiology of obesity seen in some individuals with type II diabetes mellitus (page 868).

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 am to 4.00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. Devi
8 September 1998

JAMES C. HOUSEL 9/14/98
SUPERVISORY PATENT EXAMINER